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10/564,932	01/13/2006	Frank Theobald	03/058 LTSBOE	4048

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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,932	THEOBALD ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-12 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-12 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 6-12 and 14-18 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments mailed on November 26th 2008 is acknowledged. Claims 1-3, 14 and 16-17 are amended and claims 4-5 and 13 are cancelled. Claims under consideration in the instant office action are claims 1-3, 6-12 and 14-18

Applicants' arguments, filed 11/26/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

This rejection is necessitated by the newly submitted claims filed on 11/26/2008

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6-12 14-16 and 17-18 under 35 U.S.C. 103(a) as being unpatentable over Beier et al. (WO 03/015779 as translated by US 2004/0247656) in view of Zierenberg et al, (US 5112842) and Patel et al (WO 96/39136)

.Beier et. al teaches an active-ingredient containing matrix-controlled transdermal therapeutic system (TTS) for the use of pramipexole, ropinirole, pharmaceutically acceptable salts thereof or pharmaceutically acceptable derivative thereof (abstract). Beier et al. teaches a transdermal therapeutic system for the administration of pramipexole comprising an (i) an active ingredient-impermeable cover layer (ii) **a plurality** of active ingredient containing matrix layer (iii) a peel-off protective layer. Beier teaches that a matrix-TTS comprising pramipexole and ropinirole as active ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on

polyacrylates, especially solvent-containing polyacrylates or an polyisobutylene is used [0015]. A matrix-TTS according to Beier consists of an impermeable cover layer, one or more self-adhesive matrix layer(s) containing the active-ingredient and where applicable permeation enhancers/solubilizer, or one or more matrix layer(s) that are coated with a pressure-sensitive adhesive, and a peel off protective layer and the active ingredient contained in the matrix is pramipexole, ropinirole its salts or derivatives [0016]. The amount of pramipexole, ropinirole, salts or derivatives used in the transdermal therapeutic system of Beier ranges from 2-15% by weight of the matrix [0018].Beier teaches that active ingredient to be pramipexole, ropinirole or pharmaceutically acceptable salts of pramipexole or derivatives, solvates with the active ingredients such as hydrates and alchoholates [0017] Beier teaches that for pressure-sensitive adhesive layer, a pressure-sensitive adhesive based polymer such as polyurethane, polyisobutylene, polyvinylether, silicone, polyacrylate or a mixture thereof can be selected [0020] For the matrix, matrix formers customary in medicine are used e.g. polyacrylates and polyisobutylene and the matrix formers based on polyacrylates may be any desired homopolymers, copolymer or tetrapolymer consisting of various acrylic acid derivative, where applicable with vinyl acetate [0021-0022]. Beier teaches various monomers to be used in his invention which includes esters of acrylic and methacyrlic acids such as butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, etc that may be polymerized individually or in admixture [0024]. In addition functional monomers that are compolymerisable with the acrylates and methacyrlates include hydroxyethyl acrylate, hydroxypropyl acrylate can be used too[0025], Further more

Beier teaches examples wherein the composition of a self-adhesive matrix transdermal therapeutic system for pramipexole includes pramipexole , Copherol and Durotak 2287 [0030] and [0048]. *Durotak 2287 is the polymer recommended by the applicant in the instant specification and used in the instant examples (page 7, line 34 to page 8. line 5 , example 1 and 2 on page 12 of instant application).*

The teachings of Brier differs form the instant application in that Brier as silent as to the Pramipexole being in the form of and S (-) enantiomer, finally the flux rate greater than 5 μg/cm^2 hr or a delivery rate of pramipexole of 0.5-4.5 mg/ day.

These deficiencies are taught by Zierenberg et al and Patel et al.

Zierenberg et al teaches transdermal administration of 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole (Pramipexole) or the (-) enantiomer thereof and transdermal systems containing these active substances (abstract). Zierenberg teaches that transdermal administration of Pramipexole, doses of 2 mg per day can be administered without an orthostatic side effects occurring in the patient, which corresponds to 10 times the amount which can usually be administered by oral application of the substance (col.1, lines 30-38). Zierenberg additionally teaches that although the solution to his invention is not limited to the use of a specific transdermal therapeutic system, provided the system ensures an adequate release of active substance-systems which have an active substance reservoir consisting of an emulsion polymerized polyacrylate are preferred according to his invention. Using such systems Zierenberg teaches that it is possible to administer 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothaizole or the (-) enantiomer thereof in a dose of 0.5-5 mg per day

without any orthostatic side effects being observed (col.1, line 49 to col.2, line10, claim 9). Zierenberg additionally teaches that his system consists of a backing layer which is impervious to the active substance and is simultaneously as a covering plaster to secure the system to the skin, a reservoir containing the active substance and a removable protective film which protects the system before it is ready to be used and the preferred carrier material polyacrylate is the type marketed as Eudragit NE (a mixture of carboxyl-group-free polymerized acrylic esters and methacrylic esters). The proportion of the active substance in the reservoir is between 5-30% preferably between 7-15% by weight (col.2, line 11-23).

Patel et al. teaches transdermal formulations comprising ropinirole for use in treating Parkinson's disease (abstract). Patel teaches that the transdermal formulation offers the advantage of a more convenient mode of administration of the drug substance, thereby potentially enhancing patient compliance and in addition, drug substance is released in a more controlled fashion, over a prolonged period, offering potential therapeutic advantages (page 1, lines 29-32). Patel teaches that the transdermal system of his invention will provide a steady rate delivery, or alternatively a compartmentalized rate controlled system and a suitable target skin flux will be in the range of 5-25 preferably in the range of 10-15 ug/cm^2/hr (page 3, lines 10-13 and page 7, claims 2). Patel teaches the transdermal formulation to be provided in a unit dose form, in a range of dosage amounts, for instance to allow for titration of an individual patient's drug requirement and a suitable dose may be obtained by combining different strength formulation. Patel teaches a unit dose form to provide sufficient drug substance

for a 24 hour period to permit once-a-day application of the formula (page 3, lines 21-28). Patel also teaches the penetration of drug from the transdermal system of his invention over 254 hours and 96 hours in Example 3 (page 5-6) where in ropinirole free base displays a penetration of about 10-20 ug/cm^2 over 24 hours and 30-84 ug/cm^2 of the drug had penetrated over a period of 96 hours.

Both Pramipexole and Ropinirole are non-ergoline dopamine agonists commonly used in the treatment of Parkinson's disease as evidenced by D.J Brooks (J. Neurol.Neurosurg. Psychiatry, 2000; 68; 685-689) who teaches on page 687, under the heading Non-ergoline Agonists that ropinirole and pramipexole are both new dopamine both of which act as agonists of D2-type receptors. Therefore, Pramipexole and Ropinirole are functional equivalents. Additionally, Beier et al, teaches the use of these two drugs together in a transdermal system providing a suggestion that one of ordinary skill in the art could use pramipexole in place of Ropinirole in the transdermal system taught by Patel.

With regards to the limitation in instant claims 1, 14 and 18 of the concentration by weight of the pramipexole in the first and the second active-ingredient layer, Beier teaches his transdermal therapeutic system to comprise pramipexole or ropinirole at a concentration of 2-15% by weight of the matrix. Beier also teaches his system to comprise a plurality of active-ingredient containing matrix layer and absence of factual evidence to contrary, each active ingredient matrix layer suggested by Beier would comprise 2-15% of the active ingredient by weight of the matrix. Additionally, It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not

inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Because Beier teaches that a matrix-Transdermal Therapeutic System comprising pramipexole and ropinirole as active ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on polyacrylates is used, Zierenberg teaches the reduction of orthostatic side effects in delivering pramipexole as transdermal therapeutic form and Patel teaches that transdermal forms offers several advantages over oral administration such as patient compliance and controlled delivery of the drug, it would have been obvious to one of ordinary skill in the art at the time of the instant invention that transdermal therapeutic system comprising pramipexole with in an active –ingredient containing polymer layer with at least one pressure sensitive adhesive polymer. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success based on the state of the art at the time of invention that such a transdermal therapeutic system would be an effective system for delivery of pramipexole as it offers longer duration of constant delivery and higher stability.

With regards to limitations claimed in instant claim 11 wherein the drug is delivered continuously to a patients' skin over a period from 4 to 7 days, and limitations in the instant claims 1 and 12 of the active ingredient being released over a period between 24 hours after administration to 72 hours or 168 hours, designing transdermal therapeutic systems for delivery of drugs continuously for desired time period at the rate is well known in the art as evidenced by Scheindlin (Molecular Interventions 4: 308-312 (2004)) who teaches on page 308, the scopalamine patch is worn behind the ear and

releases the alkaloid for three days, preventing motion sickness without the need to swallow tablets periodically, the fentanyl patch acts for seventy-two hours, providing long lasting pain relief and an estrogen-progestin contraceptive patch which has to applied once a week. Accordingly, one of ordinary skill in the art would be able to formulate the transdermal therapeutic system for pramipexole as taught by Beier, Zierenberg and Patel to have the desired release profile ranging from once a day to once a week administration.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Claims under 35 U.S.C. 103(a) as being unpatentable over Beier et al. (WO 03/015779 as translated by US 2004/0247656) in view of Zierenberg et al, (US 5112842) and Patel et al (WO 96/39136) as applied to claims 1-3, 6-12 14-16 and 17-18 above further in view of Wick et al (US 5238944) and Venkateshwaran et al.

Teachings of Beier, Zierenberg and Patel are as discussed supra and are applied here in the same manner. The cited references do not teach the pressure sensitive adhesive monomer mixture additionally comprising vinyl acetate in a proportion of less than 25% by weight.

Wick et al. teaches pharmaceutical formulations and adhesive-coated sheet materials for transdermal delivery (abstract). In one of the embodiment of the pressure sensitive adhesive composition, Wick et al teaches the adhesive copolymer to comprise about 60-80% by weight of the hydrophobic monomeric acrylic or methacyrlic acid ester of an alkyl alcohol, 4-9% of reinforcing monomer selected from the group consisting of

acrylic acid, methacrylic acid etc. and about 15-35% by weight of vinyl acetate based on the total weight of all monomer in the copolymer.

Venkateshwaran et al. teaches a method of making a pressure sensitive matrix patch for transdermal delivery (abstract). Venkateshwaran teaches that transdermal delivery of various drugs and pressure sensitive adhesive matrix patches for transdermal delivery of such drugs are well known in the drug delivery art and these patches include pressure sensitive adhesive layer for affixing the patch to the skin and for carrying the drug or any excipients that are directly incorporated into this adhesive layer (col.1, lines 27-33). Venkateshwaran additionally teaches that the polymers used to form pressure sensitive adhesives are well known to those skilled in the art (col.1, lines 41-42)

As such, use of pressure sensitive adhesives as taught by the above references was well known in the pharmaceutical art at the time of the invention. Pressure sensitive adhesive compositions comprising co-polymers of monomeric acrylic or methacrylic acid with vinyl acetate was also known in the art at the time of the invention. Accordingly, it would have been obvious to one skilled in the pharmaceutical art to optimize the known polymers suitable for preparing pressure sensitive adhesives and its concentration to arrive at a composition of pressure sensitive adhesive layer which would provide good adhesion to the skin and optimal delivery of the drug through the skin. As such an ordinarily skilled artisan would apply the knowledge of developing an appropriate pressure sensitive adhesive as taught by Wick or Venkateshwaran to be

used in the pramipexole transdermal delivery system taught by Beier, Zierenberg and Patel with a reasonable expectation of success.

Response to Applicant's argument submitted on 11/26/2008

In light of the new grounds of rejection above, the arguments submitted on 11/26/2008 which was for the previously submitted rejection is moot.

However, examiner has still considered the arguments and finds them unpersuasive.

In response to applicant's argument that Beier does not teach the second active layer, Examiner disagrees and would like to point the Applicant to both claims 1 and 14 in Beier et al which recites in section (ii) a self-adhesive active -ingredient containing matrix layer or a **plurality of active-ingredient-containing layer** which reads on the instantly claimed 2nd active layer.

In response to applicant's argument that Patel et al (WO 136,) does not teach administration over 24 hours, Examiner would like to refer them example 3 on page 5 of WO 136, which teaches the experiment where in the penetration over 96 hours was studied. Although the formulation was designed to be used as a once a day application, the results suggest the use of the patch for more than 24 hours.

In response to applicant's arguments against Beier, Zierenberg and Patel references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For example. In the instant case, (i) although Beier

dose not specifically teach the pramipexole being in the S (-) enantiomer form, Zierenberg teaches this limitation. (ii) Although Beier does not teach the flux rate of the active ingredient release, this limitation is taught by Patel et al. As such In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). All the three references here are drawn towards the same art which is transdermal delivery of pramipexole or the functionally equivalent ropinirole. Accordingly, an ordinarily skilled artisan in the pharmaceutical arts at the time of the invention would be motivated to combine the teachings of these three references to arrive at the instant invention.

Applicant's arguments of unexpected results has been considered but not found to be persuasive. Although the figures 1 and 2 and example 3 on pages 12-13 of the specification shows that inventive two layered TTS provides a flux rate greater than that of the single layered TTS. Applicant fails to provide the advantage of formulation 2 since their conclusion merely states that the in-vitro investigation shows that TTS formulations composition at least one active ingredient-containing layer with 10-40% weight of pramipexole in the form of the base are suitable for continuous transdermal administration for up to 7 days (page 13, lines 11-18). Additionally, Patel et al teaches

that a flux of 10-20 ug/cm^2 of the base drug of ropinirole which is a functional equivalent of pramipexole penetrated over a period of 24 hours.

Conclusion

Claims 1-3, 6-12 14-16 and 17-18 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614